REMARKS

Claims:

Reconsideration of the rejections is respectfully requested.

The status of the claims is as follows:

Amended:	43
Pending:	43-74

The number of total claims and of independent claims remains the same or less than the amount for which fees were previously paid

The Applicants respectfully submit that the Amendment meets the requirements of 37 CFR 1.116 since the Amendment places the claims in condition for allowance. Accordingly, Applicants respectfully request entry of the Amendment.

The Applicants have modified claim 43 without prejudice or disclaimer of the subject matter therein. Moreover, Applicant reserves the right to prosecute, in one or more patent applications, the canceled claims, the claims to non-elected inventions, the claims as originally filed, and any other claims supported by the specification. Any amendments made herein to the claims were made to solely expedite or otherwise facilitate prosecution and were not made nor should they be construed to have been made to overcome any issue of unpatentability of the claims as they existed prior to such amendments.

The claims have been amended to more clearly define the invention. Support for the amendments is apparent, and no new matter is added.

Claim Rejections - 35 U.S.C. §112, First Paragraph

Claims 43-45, 48-65 and 68-73 stand rejected under 35 U.S.C. §112, first paragraph based on assertion that the claims contained subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. In particular, the Examiner objected to the recitation of the third bridging structure in claim 43.

Without conceding the correctness of the rejection, Applicants have amended claim 43 so that the disputed recitation is now absent in the amended claim. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph are respectfully requested.

Claim Rejections - 35 U.S.C. §102(b) - Ognyanov et al. (WO 97/45115)

Claims 43-74 stand rejected under 35 U.S.C. §102(b) as being anticipated by Ognyanov et al. The Examiner alleged that the claims were only entitled to a filing date of the instant application, i.e., January 9, 2001. As such, the Examiner asserted that Ognyanov et al. was valid prior art under §102(b).

Without conceding the correctness of the rejection, Applicants submit in light of the amendment to claim 43 (see above), the rejection under §102(b) is now rendered moot. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph are respectfully requested.

Specification:

The Examiner objected to the abstract because holes necessary to insert the page into the file go through the text.

Applicants have submitted an abstract on a separate sheet which is attached as Appendix B. Applicants submit the abstract is unchanged from the abstract as filed.

The Examiner objected to pages 23 and 25-27 due to certain handwritten notations on these pages.

Entry of the concurrently filed replacement section which is attached as Appendix A is respectfully requested. No new matter is added.

In light of these amendments and remarks, it is respectfully submitted that the Amendment should be entered, the rejections should be withdrawn, and that the application is in condition for allowance.[2]

Respectfully submitted,

Date:August 20, 2003

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[2] **Fee Deficiency**

If any additional extension is required, please consider this paper a petition for such an extension; Any fee for the extension required for consideration of this paper but not enumerated above or in a transmittal or other associated paper can be charged to Account No. 04-0480.

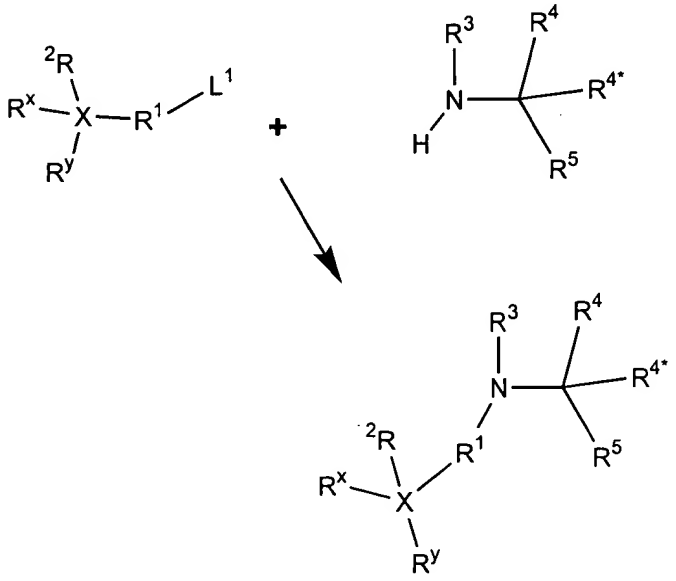
AND/OR

If any additional fee is required for consideration of this paper, please charge Account No. 04-0480.

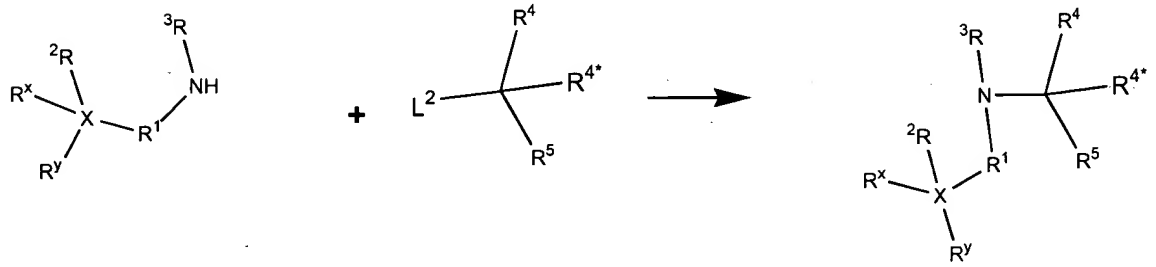
DETAILED DESCRIPTION

The compounds of the invention are generally prepared according to one of the following synthetic schemes, although alternative schemes will be recognized by those of ordinary skill.

Reaction 1

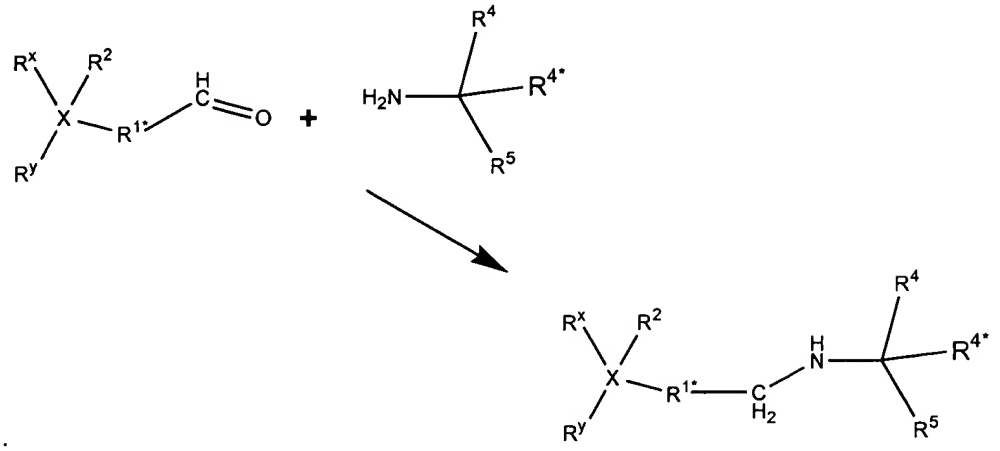


Reaction 2

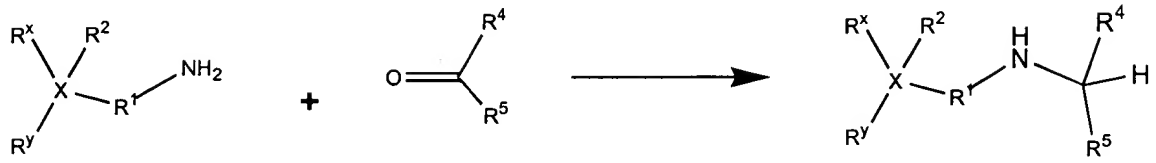


In Reaction 1 or Reaction 2, L^1 and L^2 are good nucleophilic substitution leaving groups such as a halide, especially a bromide, a tosylate, a brosylate (p-bromobenzenesulfonate), and the like. The reaction is preferably conducted in the presence of a base such as potassium carbonate or a tertiary amine such as diisopropylethylamine. Where the leaving group is a halide, the reaction is preferably conducted in the presence of an iodide salt such as potassium iodide. Suitable organic solvents include, for example, methanol, dioxane, acetonitrile or dimethyformamide. Reaction 1 is favorably conducted at a temperature range of about 50°C to about 100°C. Reaction 2 is favorably conducted at a temperature range of about 15°C to about 40°C. Avoiding more elevated temperatures helps decrease the formation of additional alkylation products. Those of ordinary skill will recognize that reaction 2 should be conducted with compounds that lack ring C.

Reaction 3



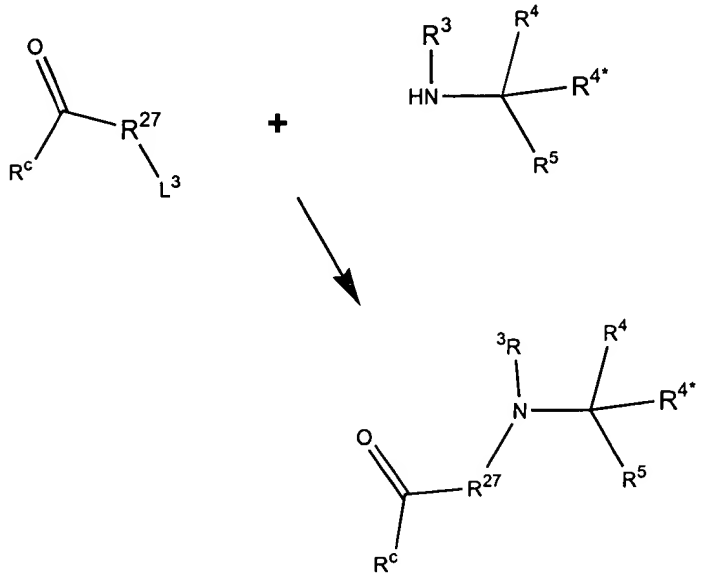
Reaction 4



In Reaction 3, R^{1*} satisfies the definition of R^1 except for the absence of the carbon that is part of an aldehyde group in the starting material. The reductive alkylation of Reaction 3 or Reaction 4 can be effected by several known methods (see, for example, "Reductive Alkylation," W.S. Emerson in Organic Reactions, Vol. 4, John Wiley & Sons, 1948, p. 174 *et seq.*) including reaction with hydrogen in the presence of a catalyst such as palladium on carbon, reaction with sodium cyanoborohydride or reaction with sodium triacetoxyborohydride when groups labile to catalytic hydrogenation are present. It will be recognized that an intermediate Schiff's base is formed in the reaction, which Schiff's base is reduced to form the linkage. The intermediate Schiff's base can be isolated and then reduced in a separate reaction. Solvent selection will vary with such factors as the solubility of the starting materials, the degree to which the solvent favors the dehydration reaction forming the Schiff's base, and the suitability of the solvent in the reduction process. Suitable solvents using catalytic hydrogenation to reduce the Schiff's base include ethanol. Suitable solvents using a borohydride to reduce the Schiff's base include alcoholic solvents such as methanol or ethanol. In some cases, a drying process can be employed during the reaction to promote the dehydration reaction that forms the Schiff's base that is reduced. Such drying processes include refluxing under conditions selected to remove water as an azeotrope or the use of molecular sieves or other drying reagents. Suitable reaction temperatures include the range from about 20°C to the reflux temperature of the solvent employed.

In Reaction 5, shown in Figure 1, R^c is independently the same as defined for R^x. The starting material **I** can be synthesized, for instance, using the chemistry of Reaction 13 (similar to Reaction 1), as follows:

Reaction 13:



, wherein R^{27} has the same definition as R^1 except that it does not include a nitrogen, oxygen or sulfur and does not include any double bonds conjugated with the above-illustrated carbonyl, and wherein L^3 is a good nucleophilic substitution leaving group such as a halide, especially a bromide, a tosylate, a brosylate (p-bromobenzenesulfonate), and the like. In Reaction 5 shown in Figure 1, R^d-NH_2 is reacted with **I** to give **II** under conditions that effect a reductive alkylation, as described for Reaction 3 and Reaction 4. R^d is independently the same as defined for R^x. Alternatively, **II** can be synthesized via Reaction 18 by reacting R^d-NH_2 with **VIII** under the conditions described for Reaction 1.

In Reaction 6, shown in Figure 1, R^e is independently the same as defined for R^x. In Reaction 6, **I** is reacted with a organometallic reagent such as an aryllithium or an aryl or arylalkyl Grignard reagent to form **III**, as described, for instance, in Section 5.1.2 of Cary and Sundberg, Advanced Organic Chemistry, Part 2, Plenum, New York, 1977, pp. 170 -180, and references cited therein. This reaction is described below in more detail for the synthesis of compound A32 (step 2 of Example 5A). Those of ordinary skill will be aware that in some cases where R^5 includes an ester, the organometallic reagent may react with the ester group; in those such cases where the yield of the desired product is too low, the solvent, the organometallic reagent or the ester substitution can be varied.

In Reaction 7, shown in Figure 1, **III** is subjected to conditions suitable for dehydration to form the double bond of **IV**. Such conditions are, for instance, those described in H. Weiland, Ber. 45: 484 *et seq.* (1912), wherein **III** is refluxed with acetic anhydride. In the illustration, the double bond forms with the adjacent carbon atom of R^{27}. The double bond will typically form with this orientation where R^c and R^e are aryl or heteroaryl and the adjacent carbon of R^{27} is saturated and not fully substituted, but other orientations are possible depending on the composition of R^c, R^e and R^{27}.

In Reaction 8, shown in Figure 1, **IV** is reduced to form **V**, for instance using any of a number of known methods for reducing carbon-carbon double bonds, such as catalytic hydrogenation in the presence of an appropriate hydrogenation catalyst. An example of this process is described below for compound A4 (Example 10).

In Reaction 9, shown in Figure 1, **III** is acylated, for instance, with acetic anhydride in the presence of an acylation catalyst such as 4-dimethylaminopyridine. In this context, R^3 should not be hydrogen, though a hydrogen substituent can be restored to this position after Reaction 9 by using a suitable protecting group to mask the nitrogen.

In Reaction 10, shown in Figure 1, the ketone moiety of **I** is reduced, for instance by any of a number of known methods for selectively reducing ketones, such as reaction with lithium tri-*tert*-butoxyaluminohydride. An example of this process is described below for the preparation of compound A31 (step 1 of Example 8A).

For Reaction 11, shown in Figure 1, the hydroxyl of **VII** is replaced by a leaving group L^5, wherein the leaving group is, for instance, chloro or bromo, by reacting **VII** with, for instance, thionyl chloride or thionyl bromide. An example of this process is described below for the preparation of compound A31 (step 2 of Example 8A).

For Reaction 12, shown in Figure 1, R^f is independently the same as defined for R^x. **VIII** is reacted with R^fOH in the presence of a base such as potassium carbonate or sodium hydride. Alternatively, the thio-containing analog of **IX** can be synthesized by reacting **VIII** with R^fSH. An example of this process is described below for the synthesis of compound A31 (step 3 of Example 8A). The transformations of Reactions 11 and 12 can be conducted in a single pot, for instance by a Mitzunobu reaction such as described in Examples 8C, Step 1 and 8D, Step 2. Alternatively, **VII** can be directly reacted with an aryl halide or chloride, preferably an aryl fluoride or chloride, to form **IX**, such as is described in U.S. Patent Nos. 5,166,437 and 5,362,886. It will be recognized that typically the aryl halide used in this reaction will typically have an electron-withdrawing group that facilitates the reaction, such

as a trifluoromethyl or nitro group in the para position. 1-fluoronaphthalene is also suitable for this reaction, since the ring fused to the fluoro-substituted ring is the electron withdrawing group.

In reaction 19, **VII** is reacted with R^dNHSO_2Ar to yield **X**, as described for example in Example 8C, Step 1. In reaction 20, **X** is coverted to **II** as described, for example, in Example 8C, Step 2.

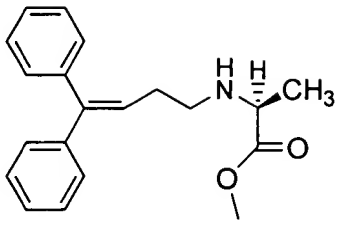
A number of other well-known synthetic approaches can be applied. For instance, acids can be formed by the hydrolysis of the corresponding esters. Amine derivatives can be formed by the alkylation of primary, secondary or tertiary amines. A number of double bond containing compounds can be hydrogenated to form the corresponding single bond. The N-oxide compounds of the invention are typically formed from the corresponding tertiary nitrogen by known methods.

In some cases, the chemistries outlined above may have to be modified, for instance by use of protective groups, to prevent side reactions due to reactive groups, such as reactive groups incorporated into heterocyclic rings or attached as substituents.

Compounds of the invention may also be prepared by adapting the classical solution chemistries outlined above into solid-phase synthetic techniques. For example, R^{13}, R^{15}, R^{16}, R^{17} and R^{20} can be residues other than hydrogen representing functionalized resin or suitably selected linker attached to functionalized resin. The linker and the functional group represented by R^5 should be stable under the conditions employed for the above-described reactions. The compounds of the invention where R^{13}, R^{15}, R^{16}, R^{17} is R^{20} is hydrogen, are then cleaved from the resin or the linker leaving the remainder of the molecule intact. For example, solid-phase synthesis of peptoids [oligo(N-substituted glycines)] using robotic synthesizer was described by Zuckermann et al., J. Am. Chem. Soc., 114, 10646-10647, (1992) and Spellmeyer et al., WO 95/04072. Under analogous conditions, acylation reaction of Rink amide polystyrene resin with bromoacetic acid in the presence of N,N'-diisopropylcarbodiimide followed by displacement of the bromine with N-substituted amine (Reaction 2) and cleavage can provide N-substituted glycinamides (R^{13} and R^{14} are hydrogen).

Using the reactions described herein, including hydrolysis of esters, alkylation of amines, or hydrogenation reactions, the following compounds of the invention have been synthesized:

A1



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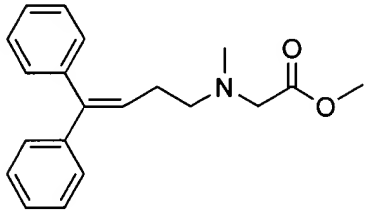

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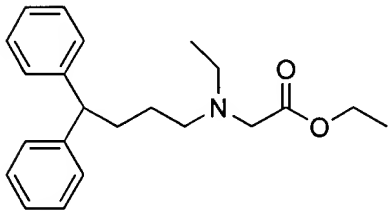

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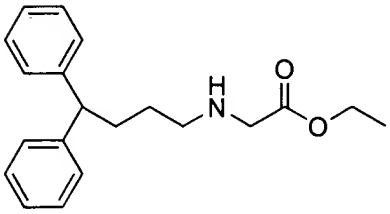

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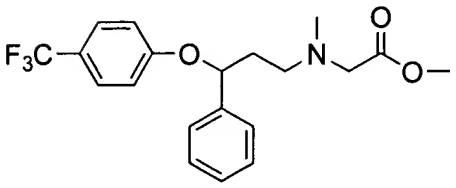

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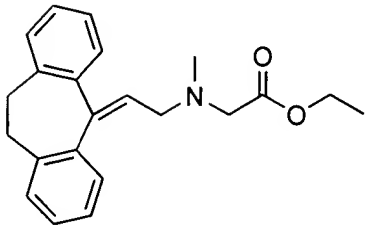

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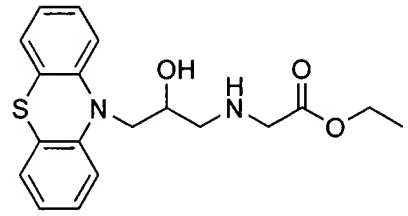

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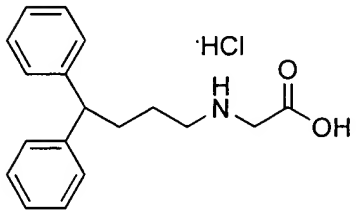

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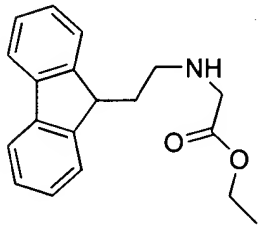

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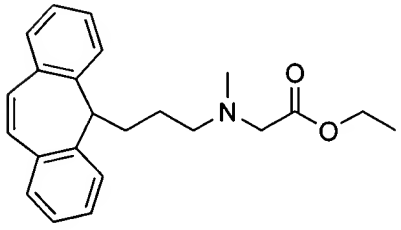

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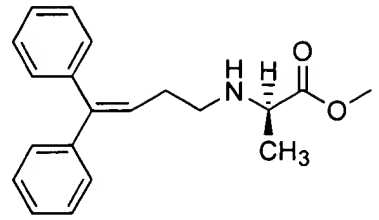

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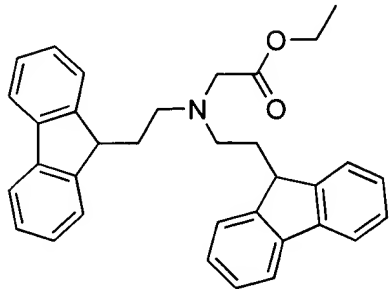

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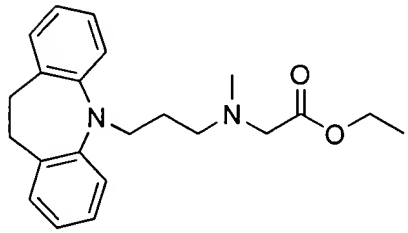

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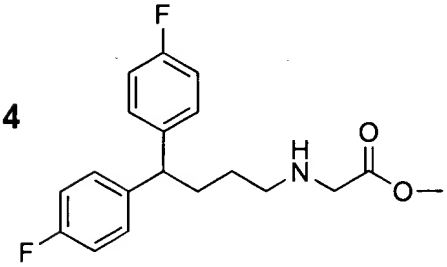

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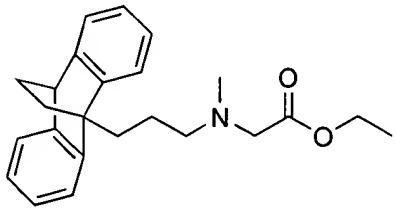

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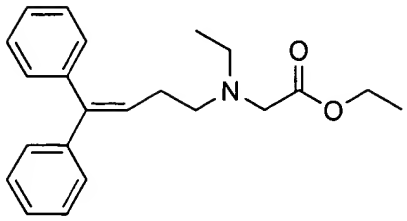

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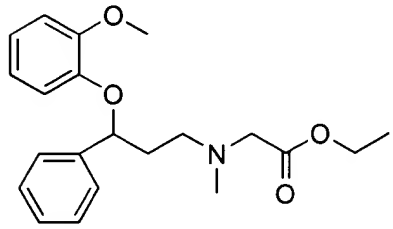

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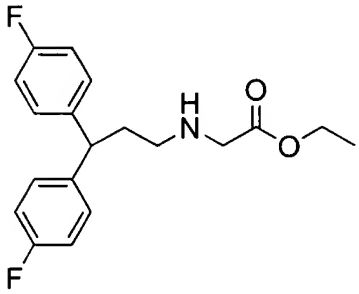

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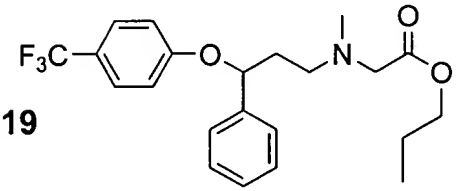

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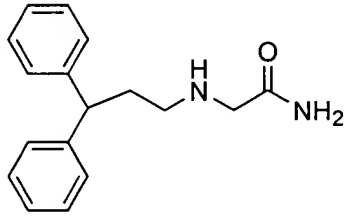

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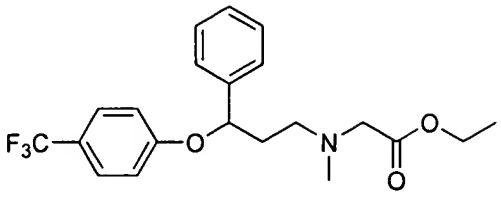

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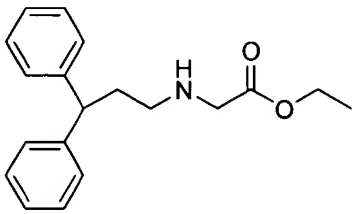

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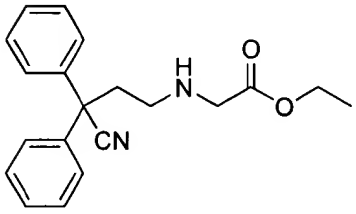

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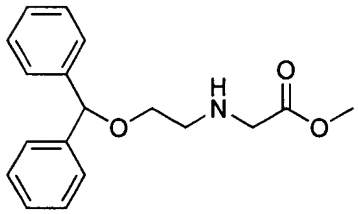

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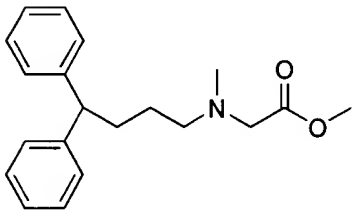

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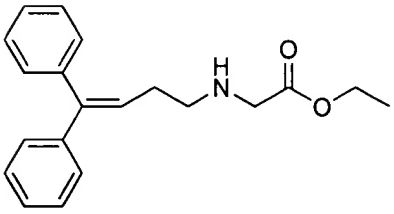

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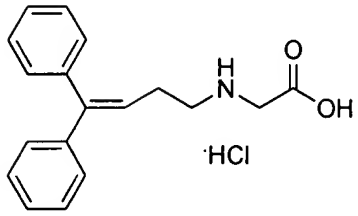

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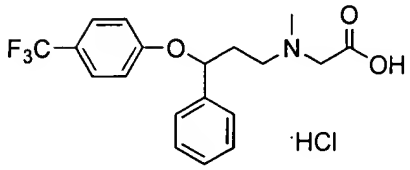

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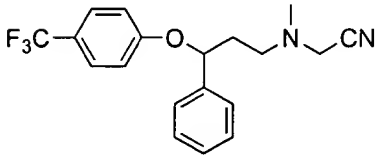

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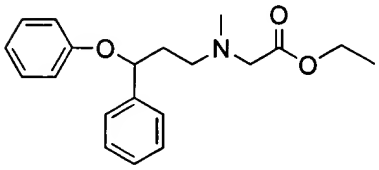

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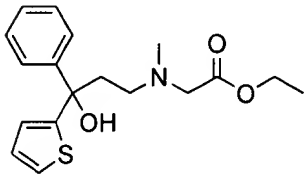

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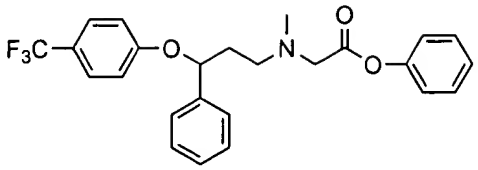

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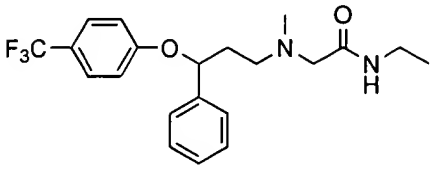

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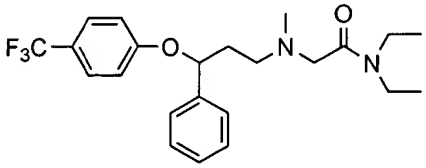

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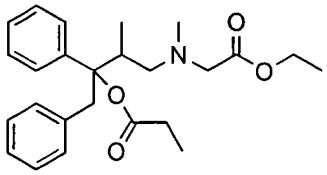

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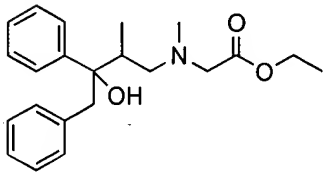

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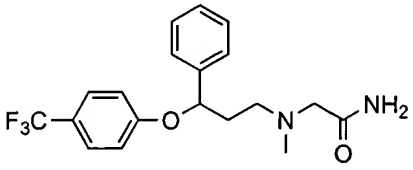

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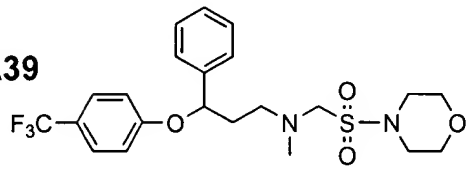

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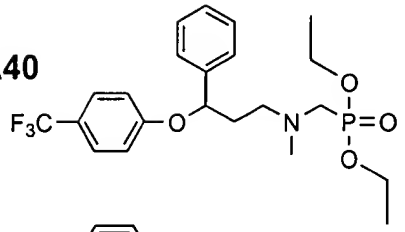

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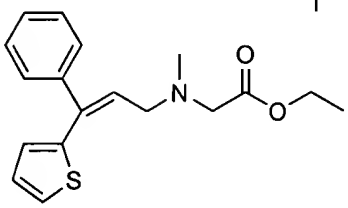

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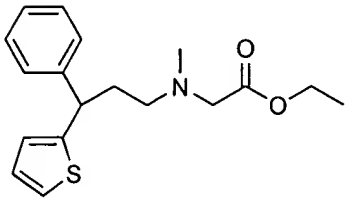

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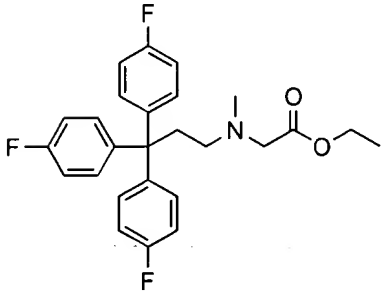

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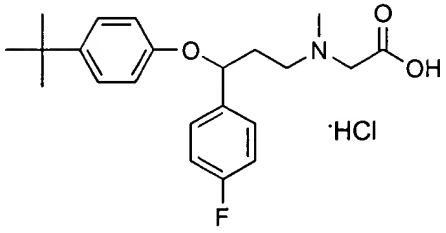

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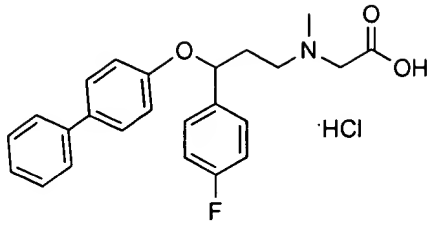

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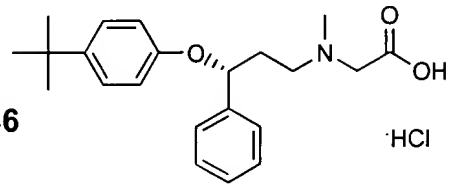

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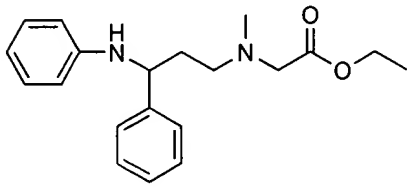

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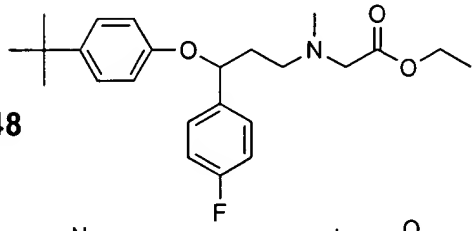

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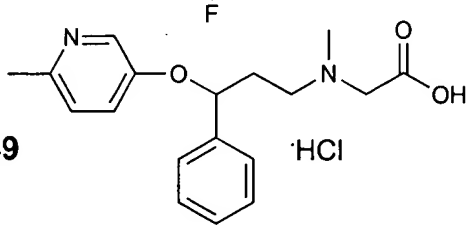

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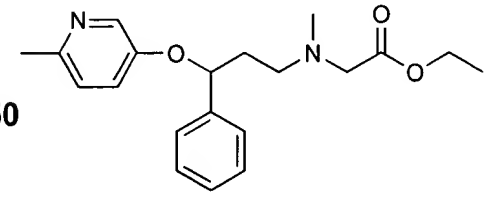

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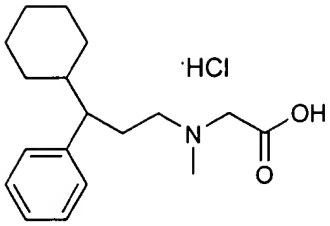

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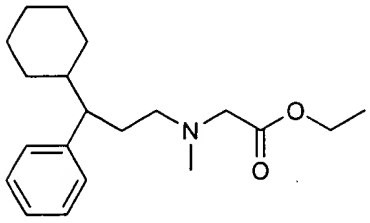

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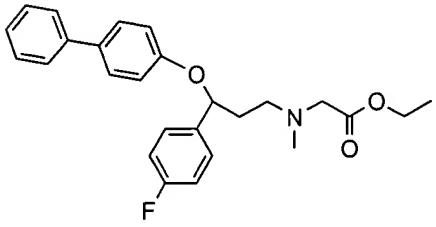

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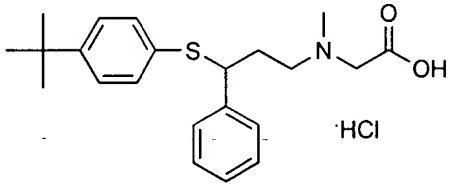

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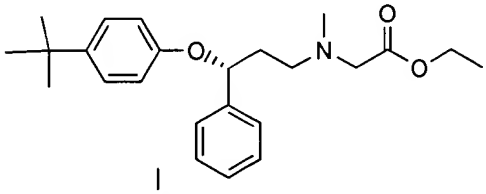

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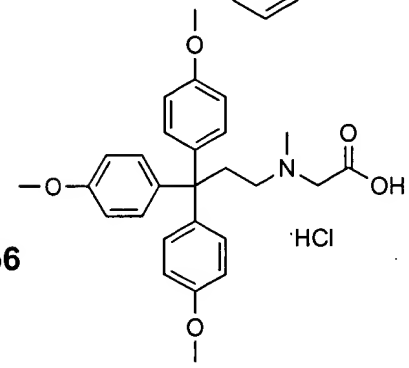

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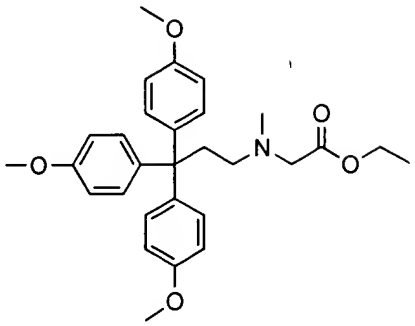

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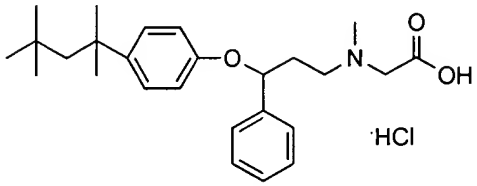

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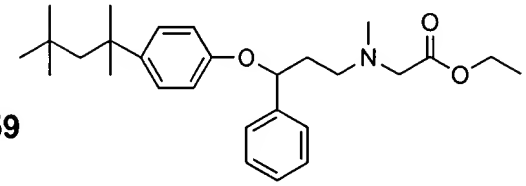

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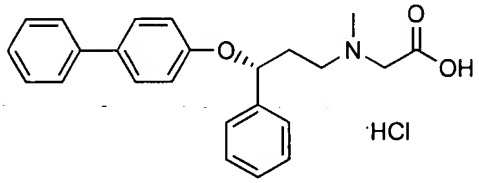

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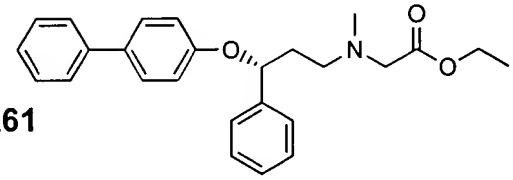

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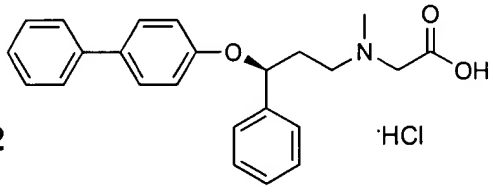

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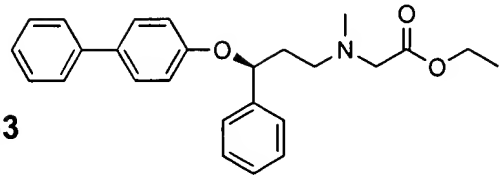

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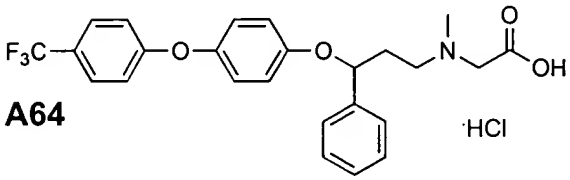

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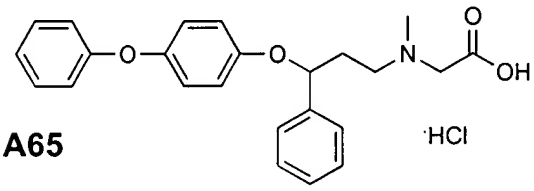

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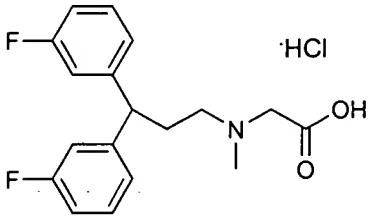

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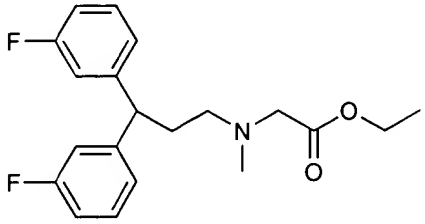

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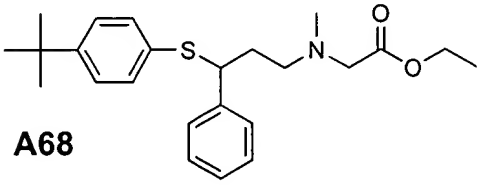

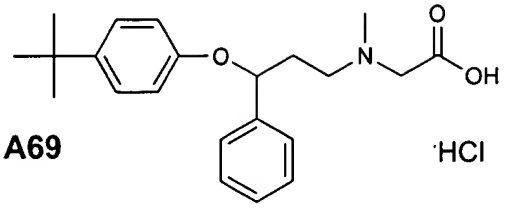

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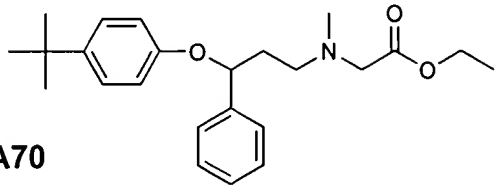

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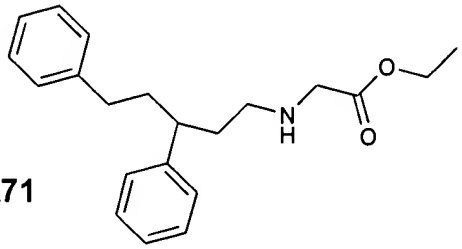

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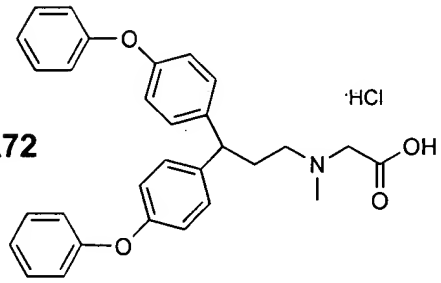

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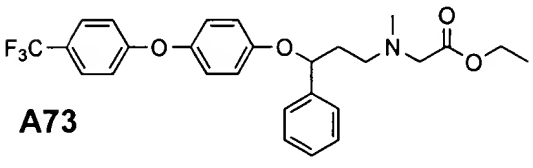

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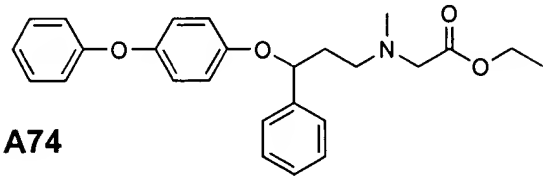

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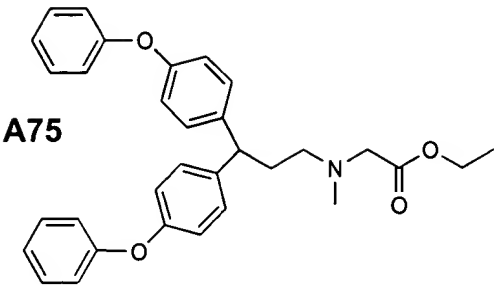

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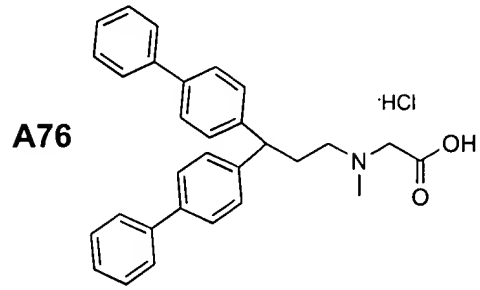

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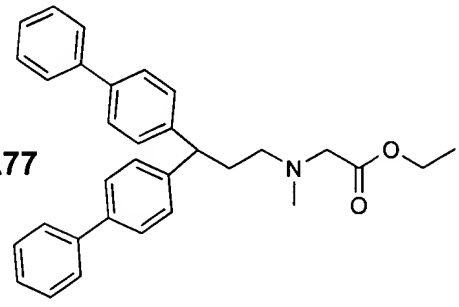

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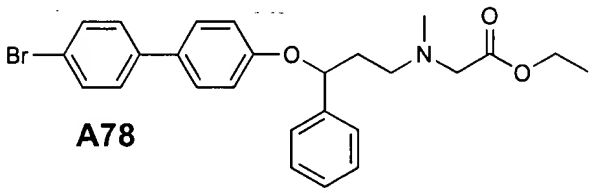

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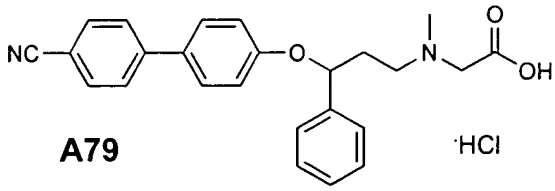

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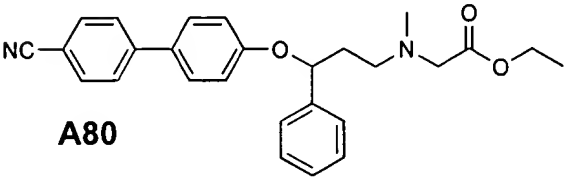

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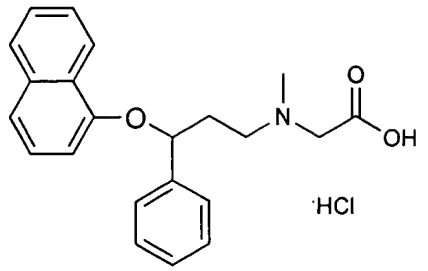

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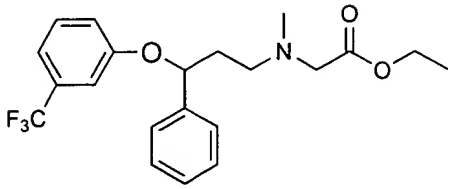

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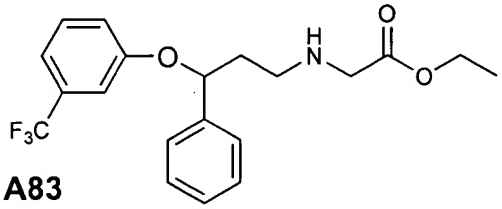

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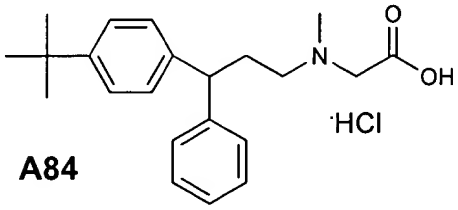

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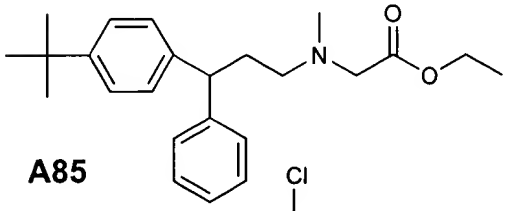

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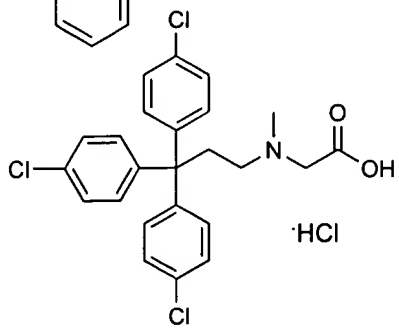

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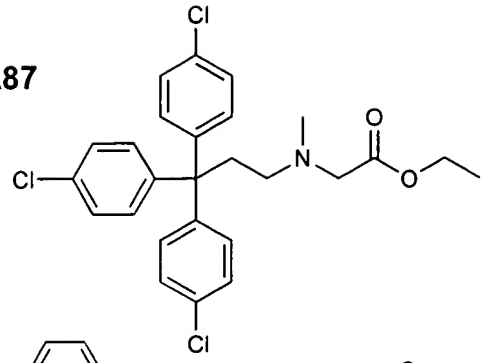

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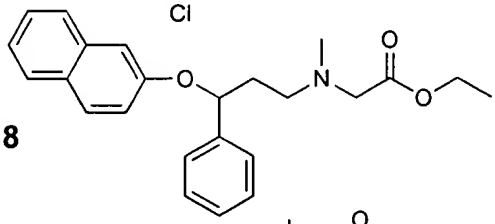

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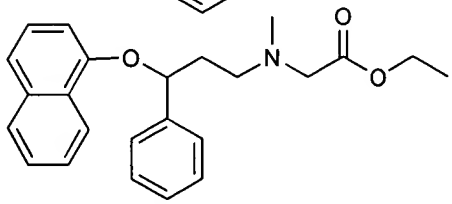

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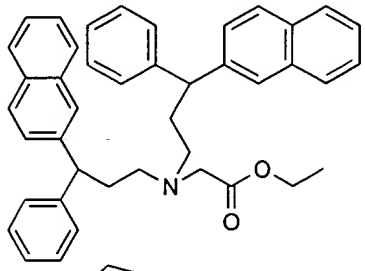

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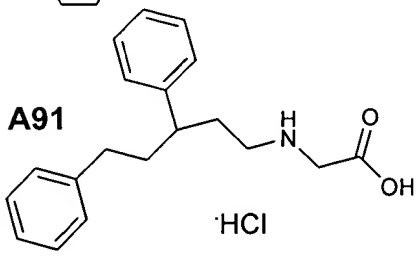

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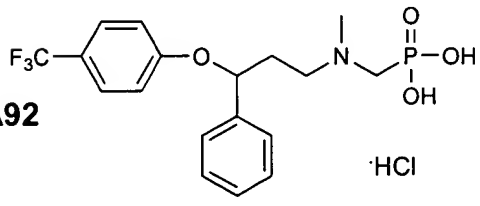

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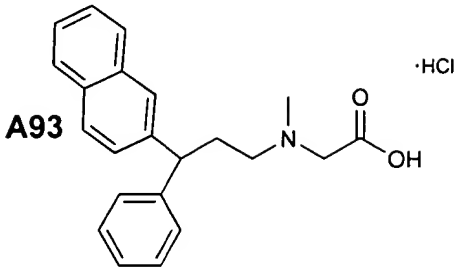

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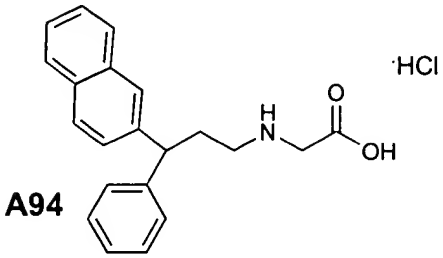

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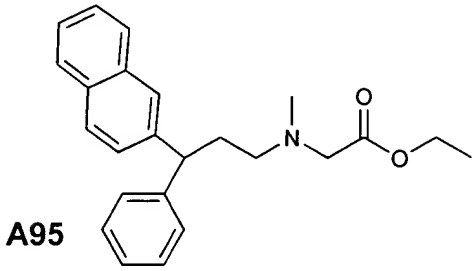

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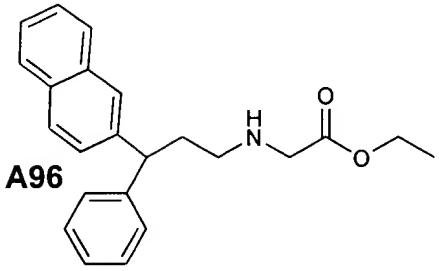

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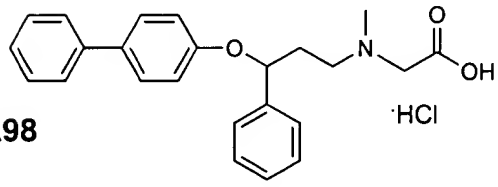

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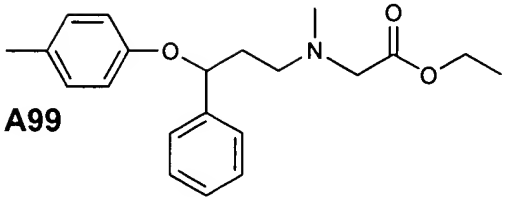

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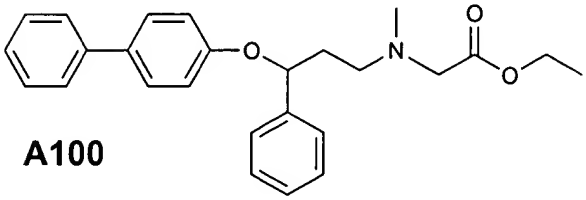

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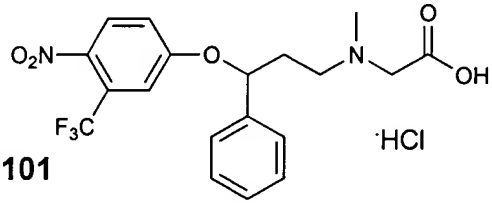

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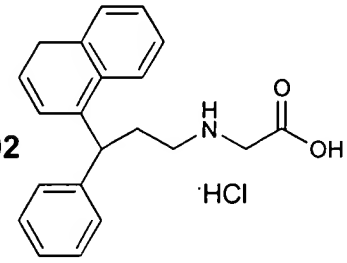

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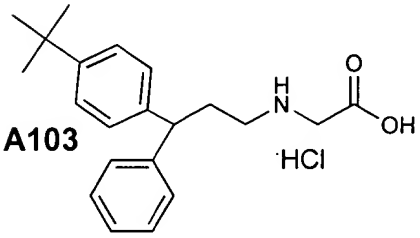

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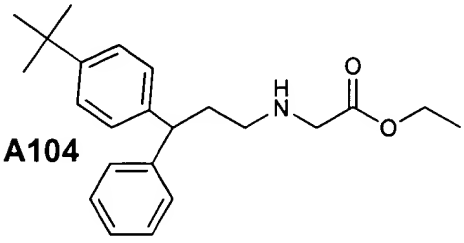

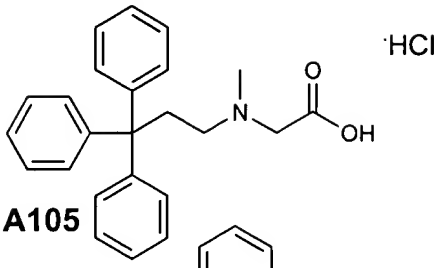

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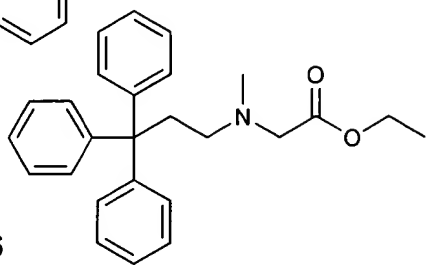

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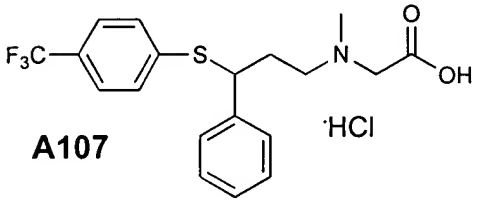

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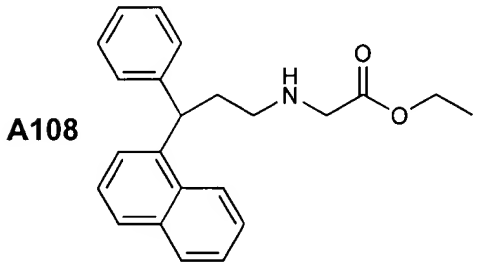

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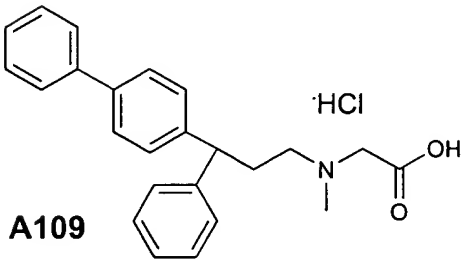

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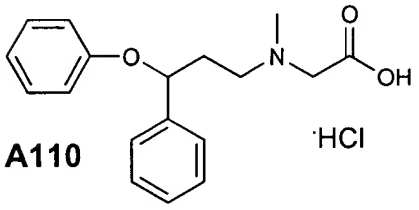

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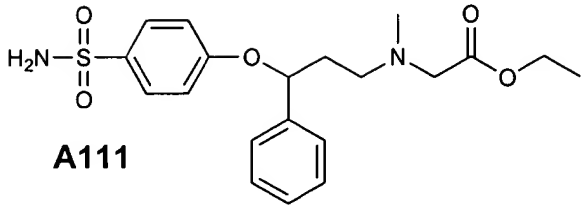

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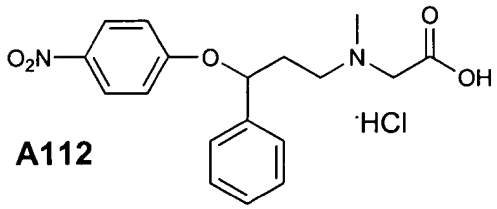

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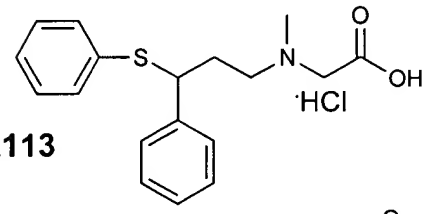

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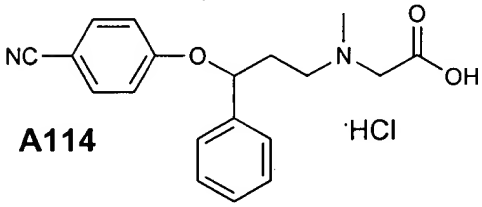

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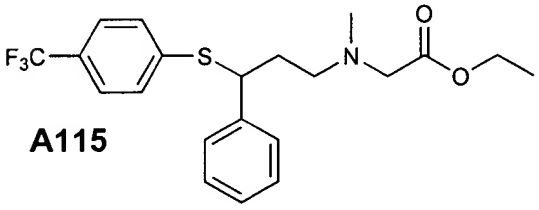

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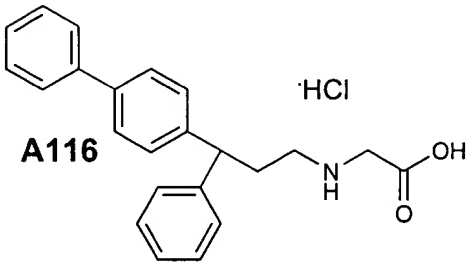

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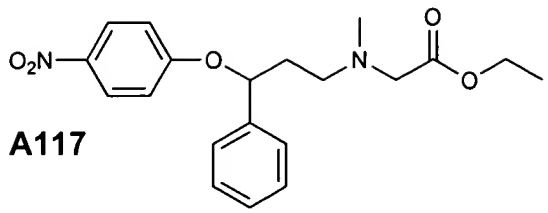

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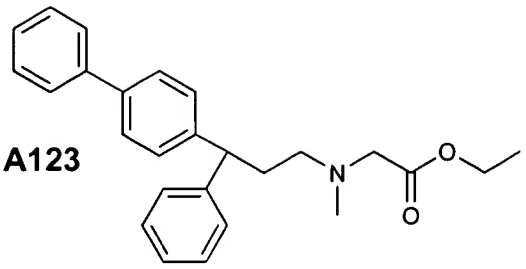

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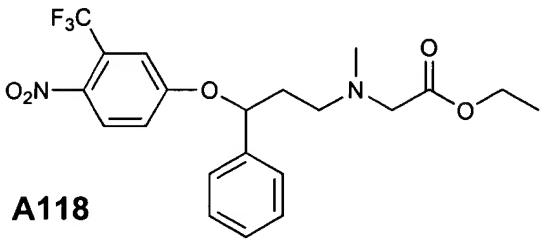

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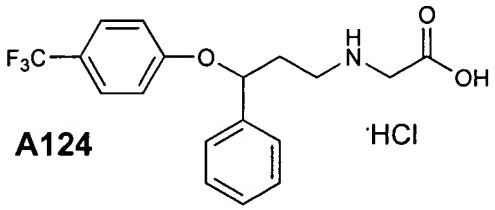

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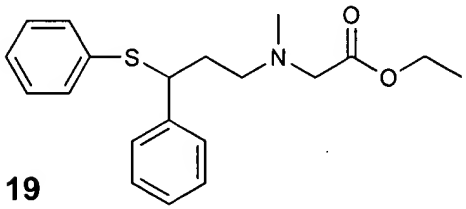

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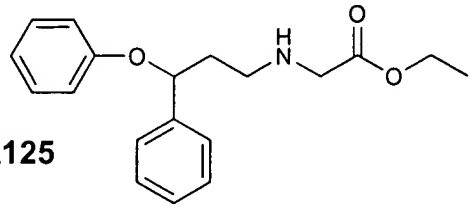

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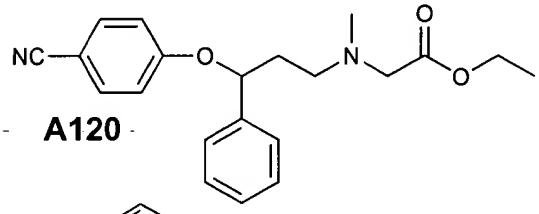

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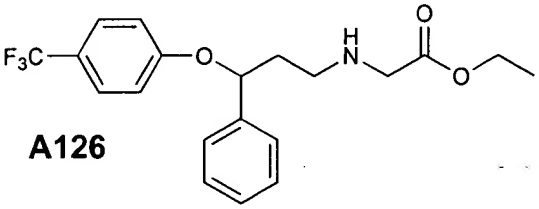

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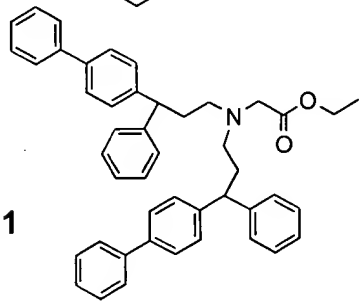

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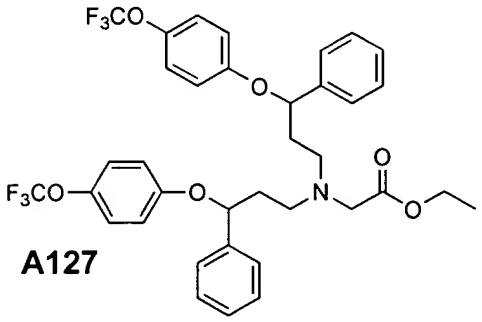

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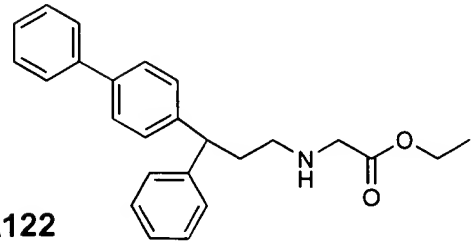

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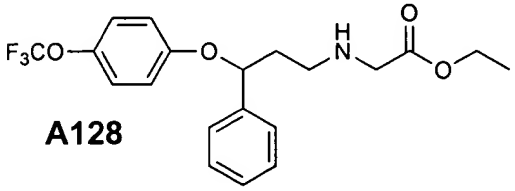

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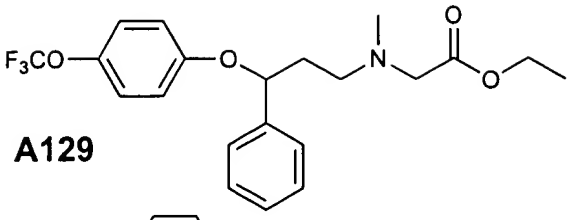

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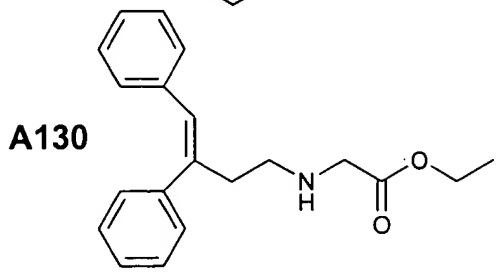

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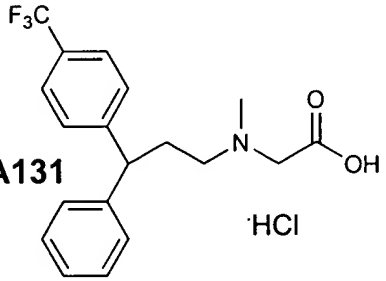

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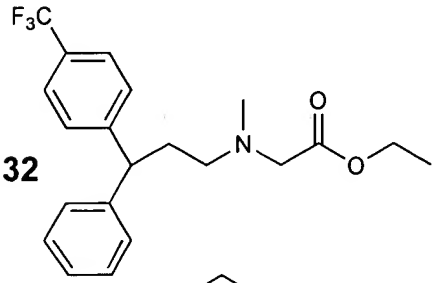

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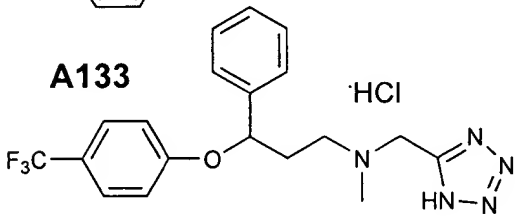

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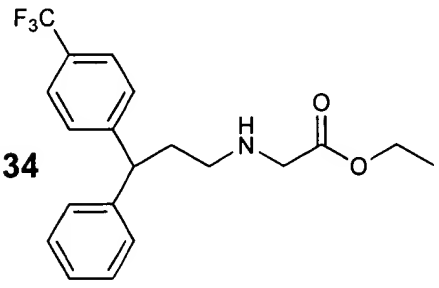

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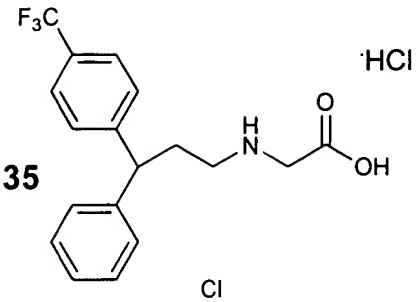

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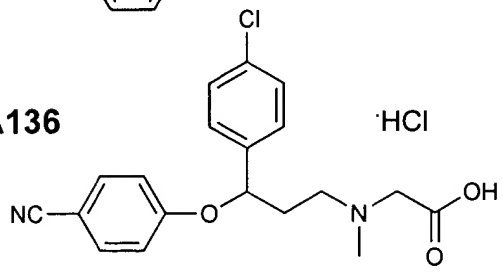

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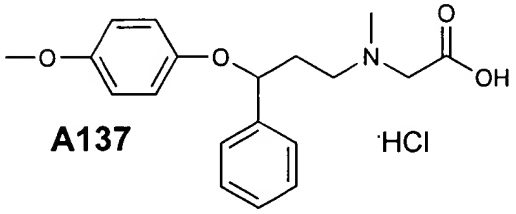

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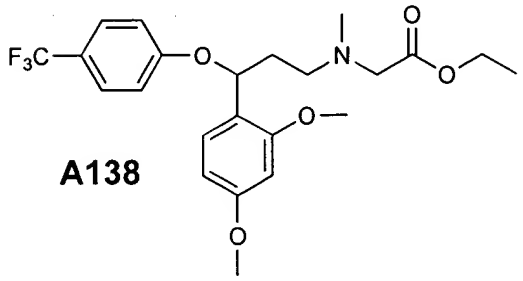

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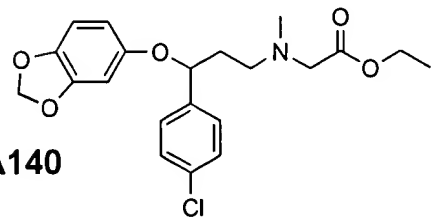

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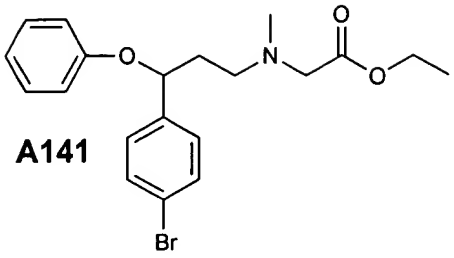

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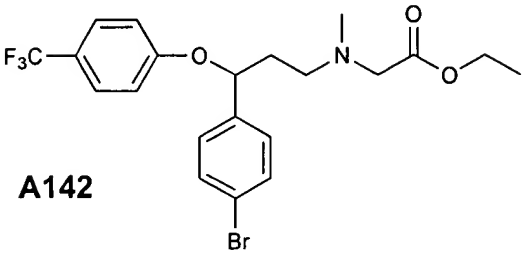

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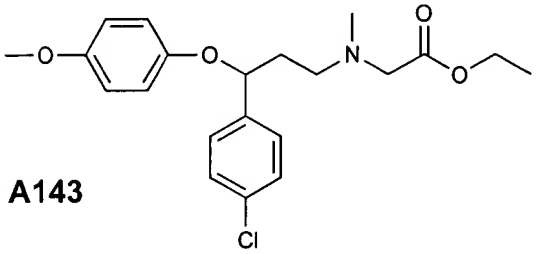

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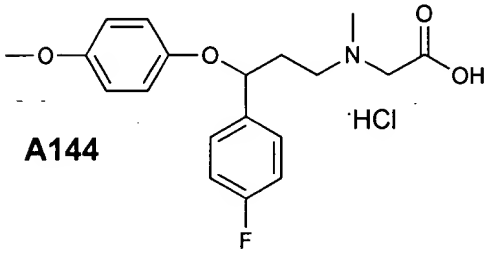

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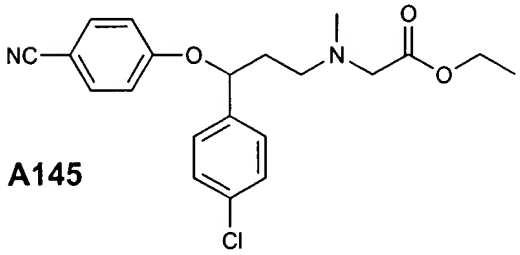

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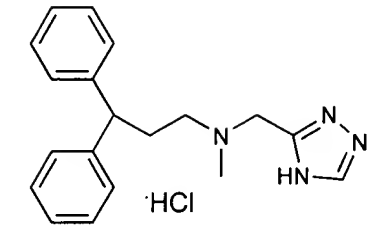

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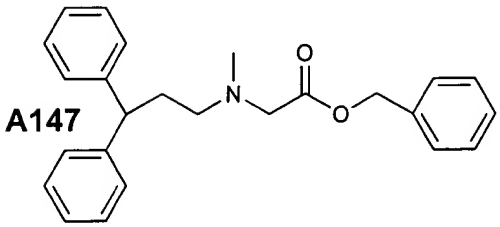

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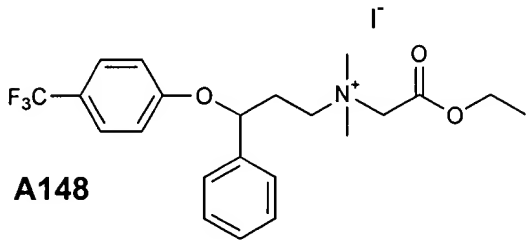

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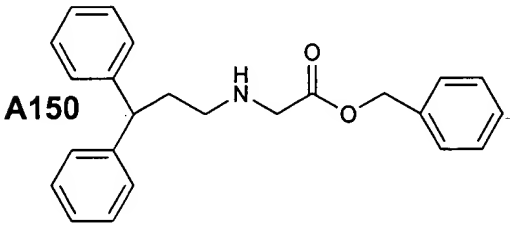

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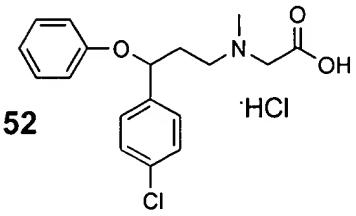

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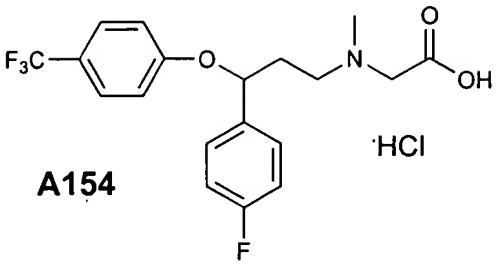

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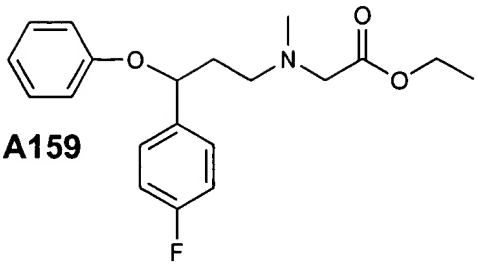

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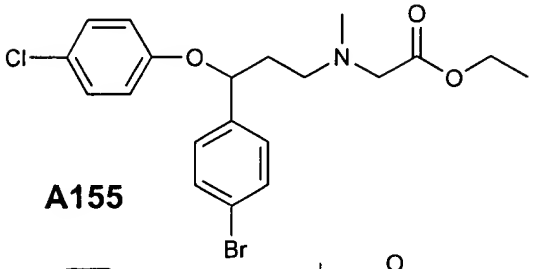

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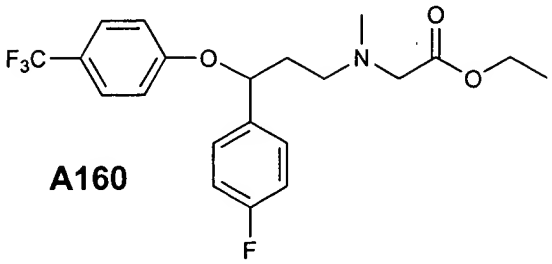

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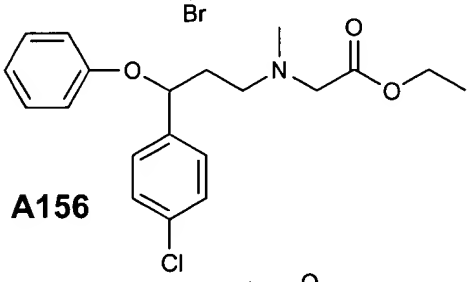

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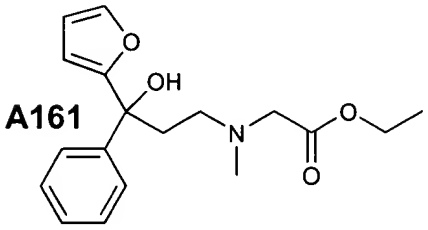

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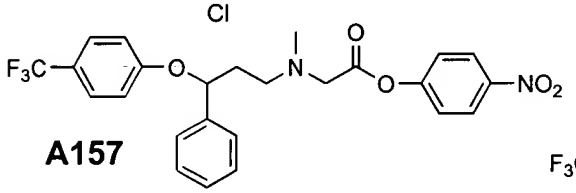

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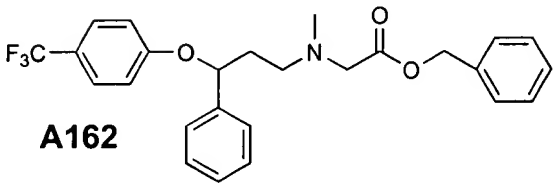

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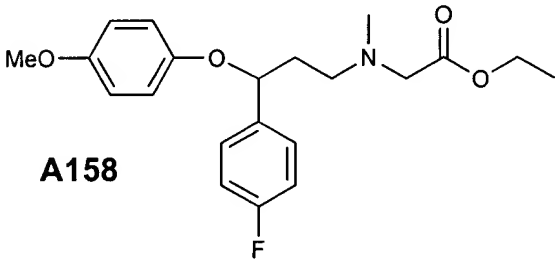

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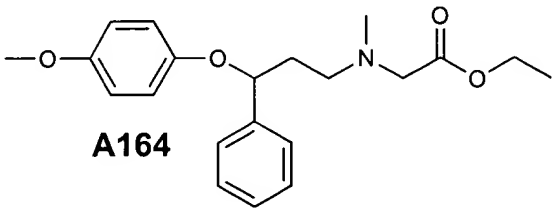

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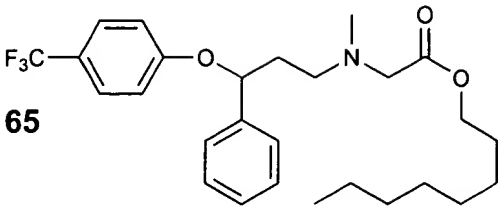

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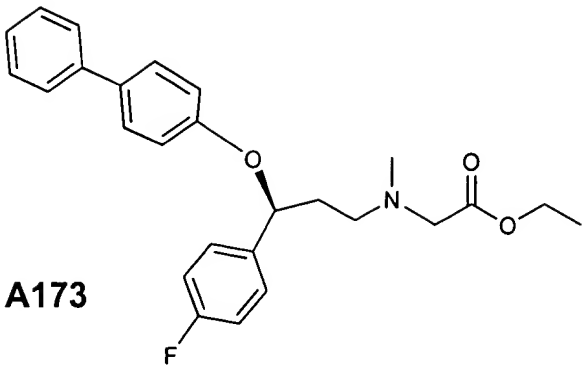

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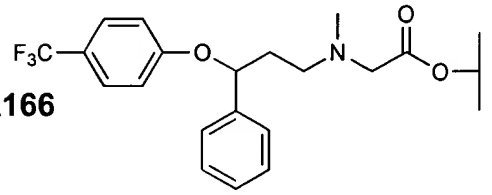

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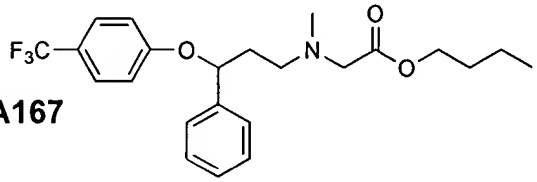

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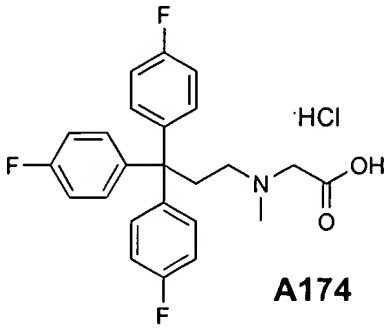

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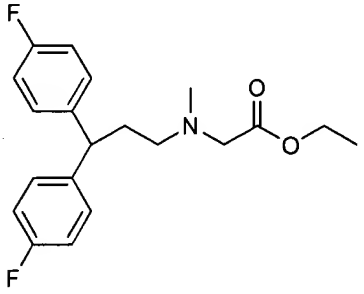

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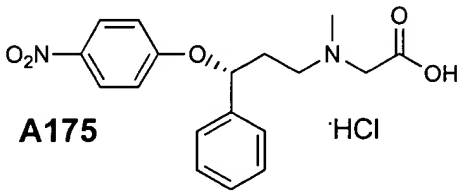

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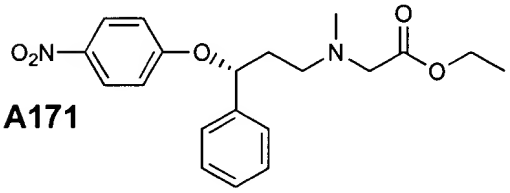

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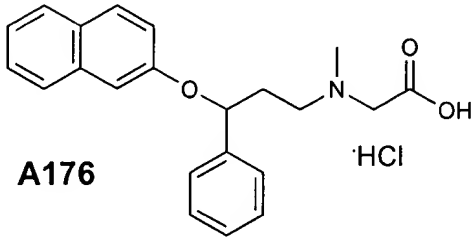

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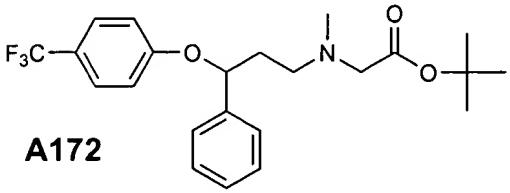

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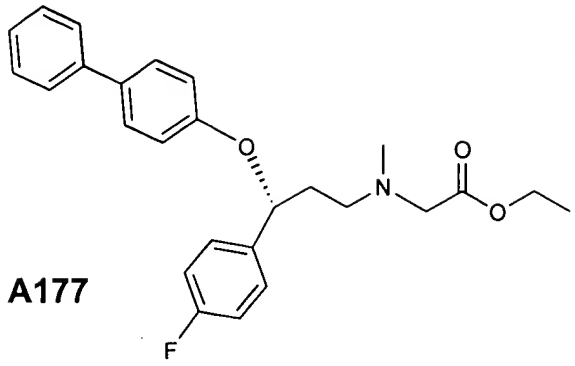

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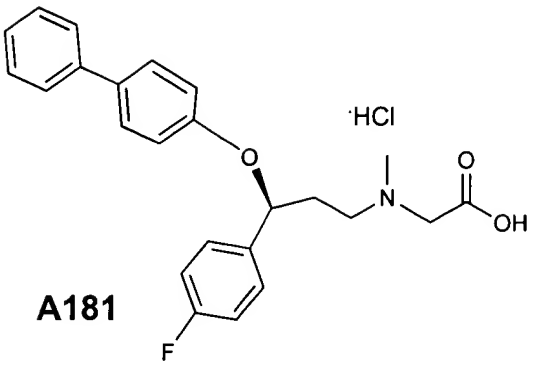

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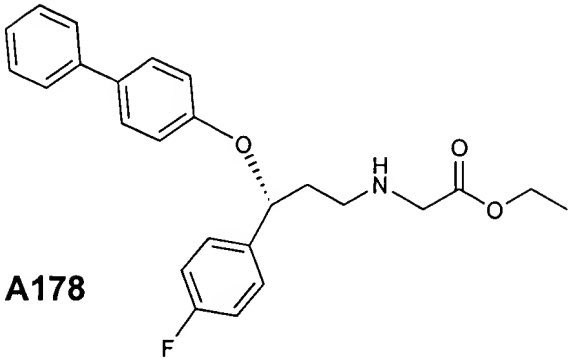

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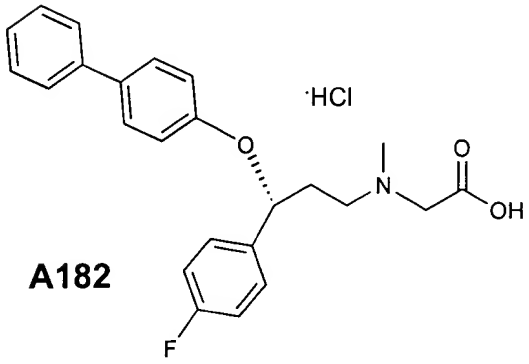

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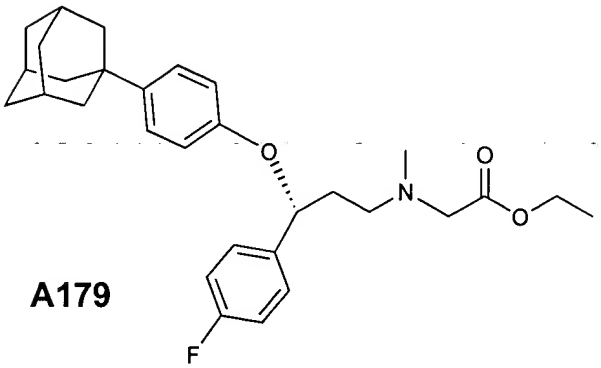

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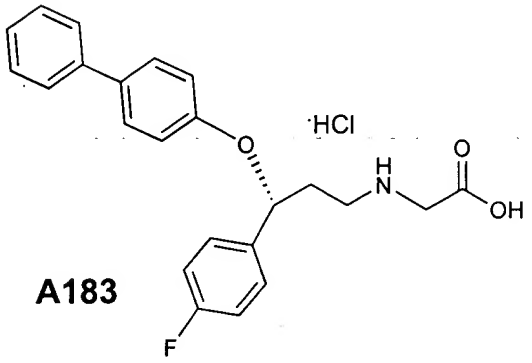

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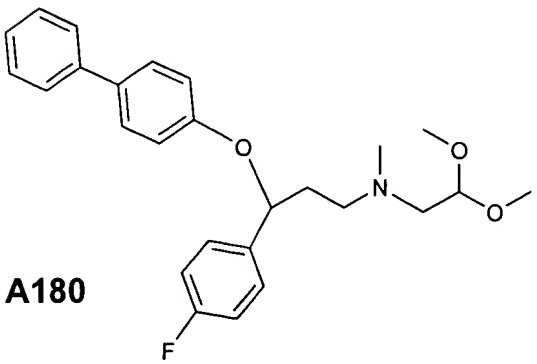

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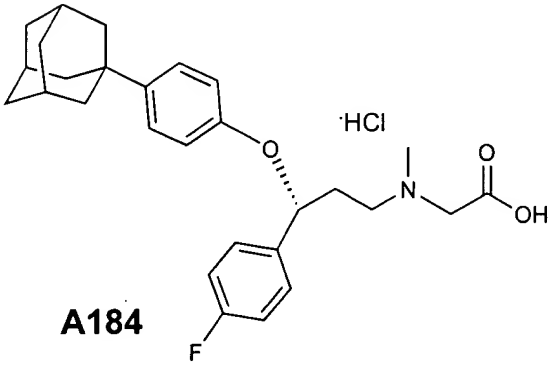

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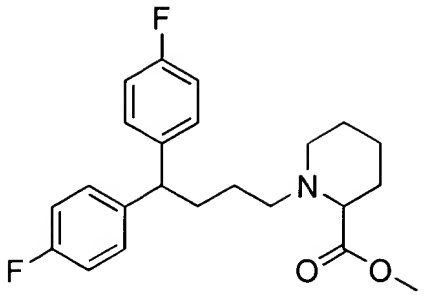

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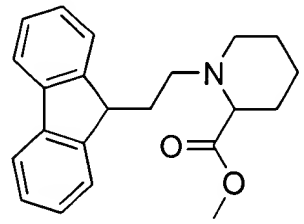

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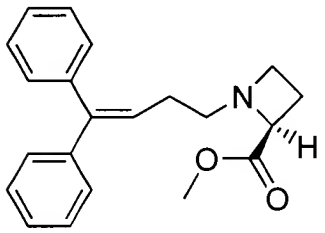

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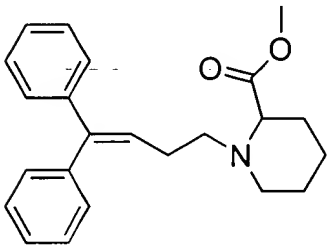

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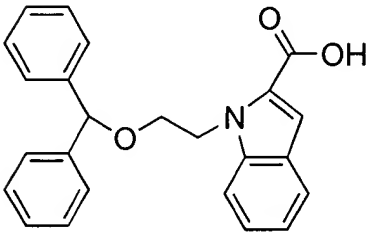

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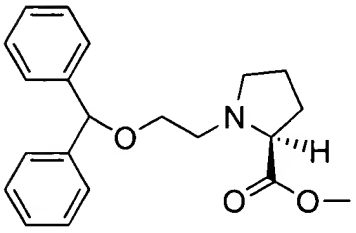

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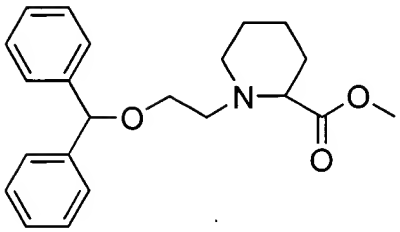

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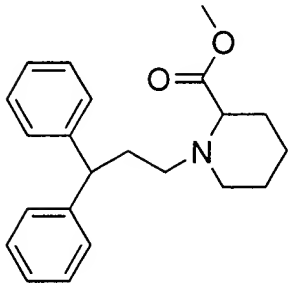

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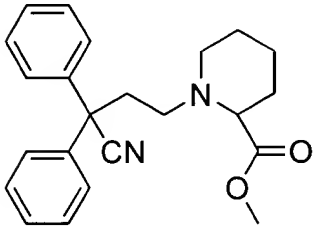

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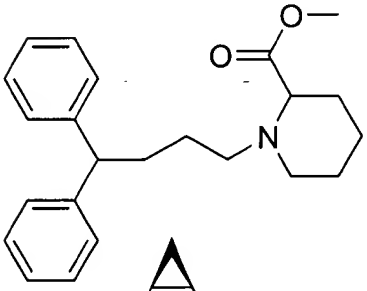

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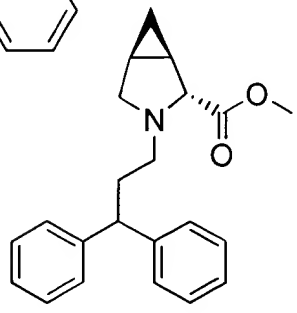

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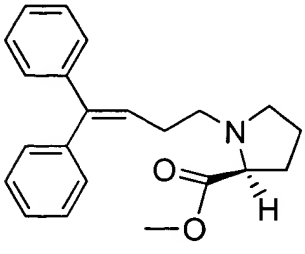

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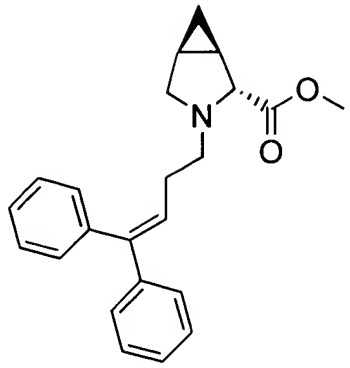

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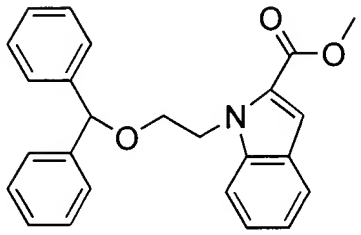

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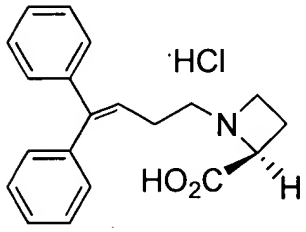

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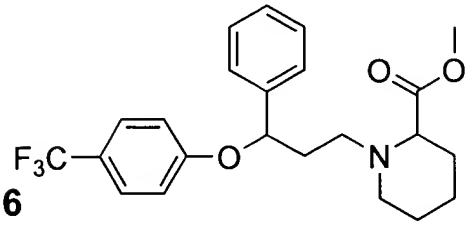

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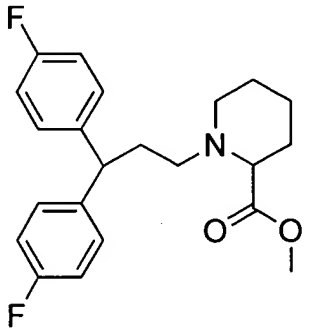

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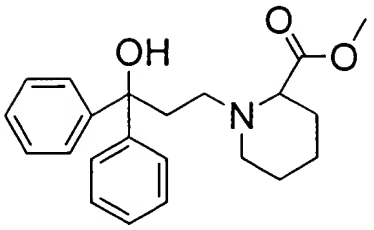

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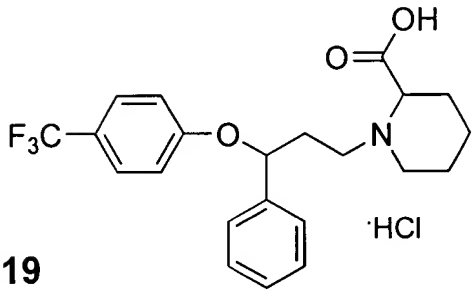

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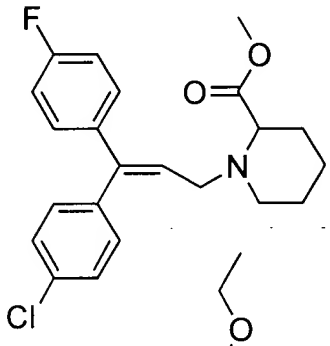

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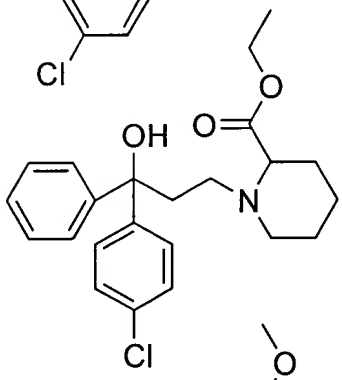

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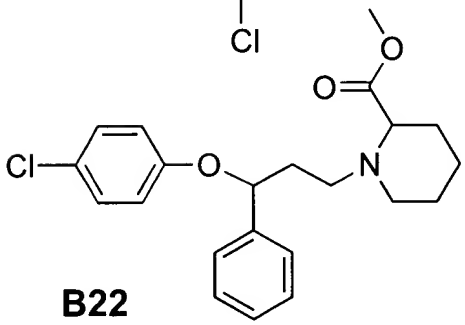
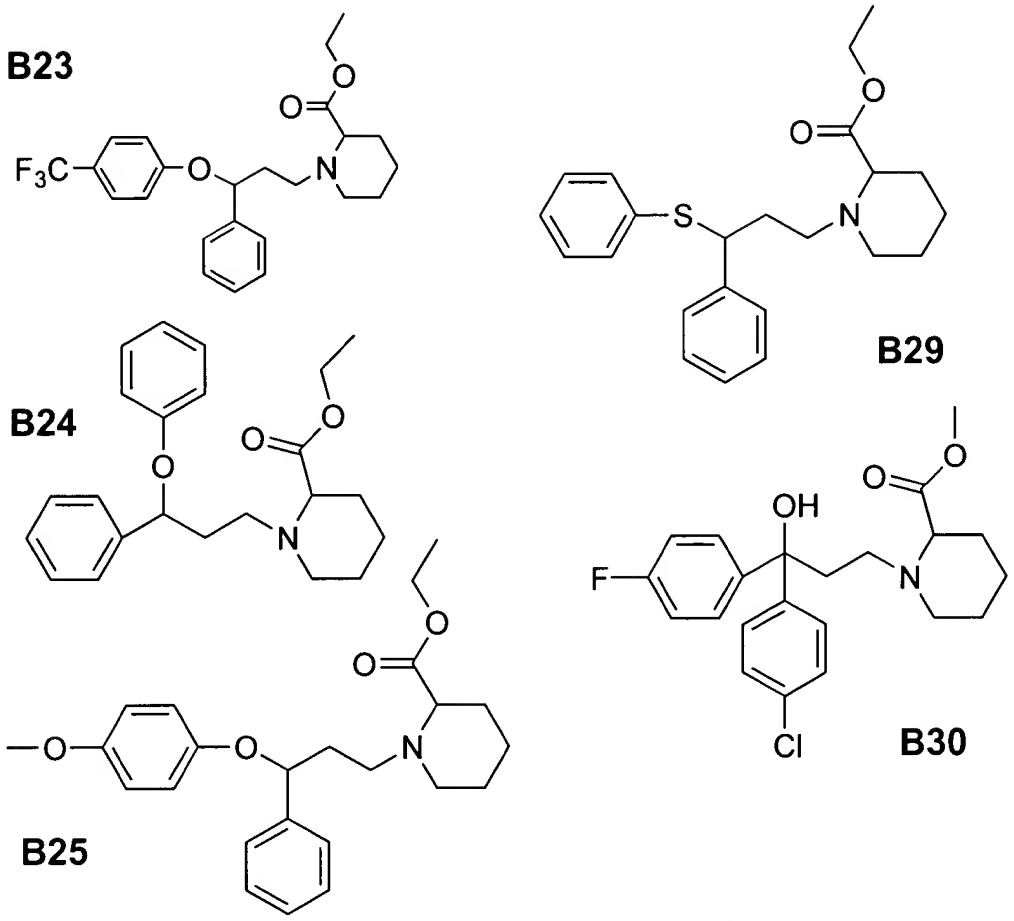




Compound A12 is a bis-alkylation byproduct of the synthesis of A9 using reaction I.

The compounds of the invention that incorporate =N-O- can be prepared, for example, by alkylating an amine (such as sarcosine or glycine) with O-(2-halogenethyl)alkanone oximes, which can be prepared by condensing alkanones with hydroxylamine, followed by O-alkylation (such as with 1,2-dihaloethane).

It will be recognized that numerous salt forms of the compounds herein described are available and suitable for use in the invention or during the synthesis of compounds of the invention. The invention contemplates that in certain instances where stereoisomers are available that one such isomer can be more active than another; in such a case, it will be desirable to isolate the particular isomeric form. The invention, of course, encompasses both the particular stereoisomers and racemic mixtures. As described herein, chemical approaches, starting with for example commercially available, optically pure starting materials (or made using enantioselective reactions), can also used to synthesize optically pure versions of the compounds of the invention. It will be recognized that such optically pure compounds are within the invention. Enantiomeric excess ("ee") can be enhanced by purification techniques such as crystallization

or chromatography on chiral supports. Enantiomeric excess can be quantitated by a number of analytic techniques including NMR, optical rotation measurements and appropriate chromatography.

Additional, related compounds are described in two U.S. Patent Applications were filed concurrently with a parent hereof as U.S. Serial No. 08/655,912 (Docket No. 317743-106, Ognyanov et al.), U.S. Serial No. 08/655,847 (Docket No. 317743-107, Ognyanov et al.), U.S. Serial No. 08/807,682 (PHARMACEUTICAL FOR TREATMENT OF NEUROPSYCHIATRIC AND NEUROLOGICAL DISORDERS, Docket No. 317743-106A, Ognyanov et al.) and U.S. Serial No. 08/807,681 (PHARMACEUTICAL FOR TREATING OF NEUROLOGICAL AND NEUROPSYCHIATRIC DISORDERS, Docket No. 317743-107A, Ognyanov et al.), which applications are also incorporated herein by reference in their entirety. Further incorporated by reference in its entirety are U.S. Application No. 08/655,912 (Docket No. 317743-103, Ognyanov et al.) and are U.S. Application No. 08/808,754 (Docket No. 317743-103A, Ognyanov et al.) the parents of the present application.

In a preferred embodiment, at least one of the following applies:

if R^{15} is hydrogen and R^1 is propylene, then at least one [preferably at least two, more preferably at least three] of the following applies (1) both R^x and R^y are not *p*-fluorophenyl, (2) one of R^x and R^y includes a heteroaryl, (3) R^y is arylalkyl, heteroarylalkyl, aryloxy, heteroaryloxy, arylmethoxy, heteroarylmethoxy, arylthio, heteroarylthio, arylmethylthio, heteroarylmethylthio, Ar-N(R^6)- or Ar-CH_2-N(R^{6*})-, (4) R^2 is R^{xa} R^{xb}-, (5) R^{2*} is not hydrogen, (6) R^3 is not hydrogen, (7) n is one, or (8) R^3 and R^4 form ring Q;

if R^{15} is hydrogen and R^1 is ethylene or X-R^1 is prop-1-enylene, then at least one [preferably at least two, more preferably at least three] of the following applies (1) an aryl of at least one of R^x and R^y is substituted with a radical different from hydrogen, (2) one of R^x and R^y comprises a heteroaryl, (3) R^y is arylalkyl, heteroarylalkyl, aryloxy, heteroaryloxy, arylmethoxy, heteroarylmethoxy, arylthio, heteroarylthio, arylmethylthio, heteroarylmethylthio, Ar-N(R^6)- or Ar-CH_2-N(R^{6*})-, (4) R^2 is R^{xa} R^{xb}-, (5) R^{2*} is not hydrogen, (6) R^3 is not hydrogen, (7) n is one, or (8) R^3 and R^4 form ring Q;

if R^5 is C(O)NH_2, then at least one [preferably at least two, more preferably at least three] of the following applies (1) an aryl of at least one of R^x and R^y is substituted with a radical different from hydrogen, (2) one of R^x and R^y comprises a heteroaryl, (3) R^y

is arylalkyl, heteroarylalkyl, aryloxy, heteroaryloxy, arylmethoxy, heteroarylmethoxy, arylthio, heteroarylthio, arylmethylthio, heteroarylmethylthio, Ar-N(R^6)- or Ar-CH_2-N(R^{6*})-, (4) R^2 is R^{xa} R^{xb}-, (5) R^{2*} is not hydrogen, (6) R^3 is not hydrogen, (7) n is one, (8) R^1 is not ethylene, or (9) R^3 and R^4 form ring Q;

if R^{13} is hydrogen and R^{14} is (3,4-dihydro-2H-1-benzopyran-4-yl)methylene, then at least one [preferably at least two, more preferably at least three] of the following applies (1) an aryl of at least one of R^x and R^y is substituted with a radical different from hydrogen, (2) one of R^x and R^y comprises a heteroaryl, (3) R^y is arylalkyl, heteroarylalkyl, aryloxy, heteroaryloxy, arylmethoxy, heteroarylmethoxy, arylthio, heteroarylthio, arylmethylthio, heteroarylmethylthio, Ar-N(R^6)- or Ar-CH_2-N(R^{6*})-, (4) R^2 is R^{xa} R^{xb}-, (5) R^{2*} is not hydrogen, (6) R^3 is not ethyl, (7) n is one, or (8) R^3 and R^4 form ring Q; and

if R^2 is phenyl, *p*-methylphenyl or *p*-methoxyphenyl, then at least one [preferably at least two, more preferably at least three] of the following applies (1) the aryls of R^x and R^y are not substituted with *p*-methylphenyl or *p*-methoxyphenyl, (2) an aryl of at least one of R^x and R^y is substituted with a radical different from hydrogen, (3) one of R^x and R^y comprises a heteroaryl, (4) R^y is arylalkyl, heteroarylalkyl, aryloxy, heteroaryloxy, arylmethoxy, heteroarylmethoxy, arylthio, heteroarylthio, arylmethylthio, heteroarylmethylthio, Ar-N(R^6)- or Ar-CH_2-N(R^{6*})-, (5) R^1 is not aminoethylene, OR^8 or SR^{8*}, (6) n is one, or (7) R^3 and R^4 form ring Q.

In one preferred embodiment of the the methods, particularly treating or preventing epilepsy or spasticity or enhancing memory, the compound conforms with paragraph (f), above.

The glycine transporter genes and their respective gene products are responsible for the reuptake of glycine from the synaptic cleft into presynaptic nerve endings or glial cells, thus terminating the action of glycine. Neurological disorders or conditions associated with improperly controlled glycine receptor activity, or which could be treated with therapeutic agents that modulate glycine receptor activity, include spasticity (Becker, FASEB Journal, 4, 2767-2774 (1990)) and pain realization (Yaksh, Pain, 37, 111-123 (1989)). Additionally, glycine interacts at N-methyl-D-aspartate (NMDA) receptors, which have been implicated in learning and memory disorders and certain clinical conditions such as epilepsy, Alzheimer's and other cognition-related diseases, and schizophrenia. See Rison and Stanton, Neurosci. Biobehav. Rev., 19, 533-552 (1995); Danysz et al., Behavioral Pharmacol., 6, 455-474 (1995).

Compounds that inhibit GlyT-1 mediated glycine transport will increase glycine concentrations at NMDA receptors, which receptors are located in the forebrain, among other locations. This concentration increase elevates the activity of NMDA receptors, thereby alleviating schizophrenia and enhancing cognitive function. Alternatively, compounds that interact directly with the glycine receptor component of the NMDA receptor can have the same or similar effects as increasing or decreasing the availability of extracellular glycine caused by inhibiting or enhancing GlyT-1 activity, respectively. See, for example, Pitkänen et al., Eur. J. Pharmacol., 253, 125-129 (1994); Thiels et al., Neuroscience, 46, 501-509 (1992); and Kretschmer and Schmidt, J. Neurosci., 16, 1561-1569 (1996). Compounds that inhibit GlyT-2 mediated glycine transport will increase glycine concentrations at receptors located primarily in the brain stem and spinal cord, where glycine acts as an inhibitor of synaptic transmission. These compounds are effective against epilepsy, pain and spasticity, myospasm and other such conditions. See, for example, Becker, FASEB J., 4, 2767-2774 (1990) and Yaksh, Pain, 37, 111-123 (1989).

The compounds of the invention are, for instance, administered orally, sublingually, rectally, nasally, vaginally, topically (including the use of a patch or other transdermal delivery device), by pulmonary route by use of an aerosol, or parenterally, including, for example, intramuscularly, subcutaneously, intraperitoneally, intraarterially, intravenously or intrathecally. Administration can be by means of a pump for periodic or continuous delivery. The compounds of the invention are administered alone, or are combined with a pharmaceutically-acceptable carrier or excipient according to standard pharmaceutical practice. For the oral mode of administration, the compounds of the invention are used in the form of tablets, capsules, lozenges, chewing gum, troches, powders, syrups, elixirs, aqueous solutions and suspensions, and the like. In the case of tablets, carriers that are used include lactose, sodium citrate and salts of phosphoric acid. Various disintegrants such as starch, and lubricating agents such as magnesium stearate and talc, are commonly used in tablets. For oral administration in capsule form, useful diluents are lactose and high molecular weight polyethylene glycols. If desired, certain sweetening and/or flavoring agents are added. For parenteral administration, sterile solutions of the compounds of the invention are usually prepared, and the pHs of the solutions are suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled to render the preparation isotonic. For ocular administration, ointments or droppable liquids may be delivered by ocular delivery systems known to the art such as applicators or eye droppers. Such compositions can include mucomimetics such as hyaluronic acid, chondroitin sulfate, hydroxypropyl methylcellulose or polyvinyl alcohol, preservatives such as sorbic acid, EDTA or benzylchromium chloride, and the usual quantities of diluents and/or carriers. For pulmonary administration, diluents and/or carriers will be selected to be appropriate to allow the formation of an aerosol.

Suppository forms of the compounds of the invention are useful for vaginal, urethral and rectal administrations. Such suppositories will generally be constructed of a mixture of substances that is solid at room temperature but melts at body temperature. The substances commonly used to create such vehicles include theobroma oil, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weight and fatty acid esters of polyethylene glycol. *See*, Remington's Pharmaceutical Sciences, 16th Ed., Mack Publishing, Easton, PA, 1980, pp. 1530-1533 for further discussion of suppository dosage forms. Analogous gels or cremes can be used for vaginal, urethral and rectal administrations.

Numerous administration vehicles will be apparent to those of ordinary skill in the art, including without limitation slow release formulations, liposomal formulations and polymeric matrices.

Examples of pharmaceutically acceptable acid addition salts for use in the present invention include those derived from mineral acids, such as hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric and sulfuric acids, and organic acids, such as tartaric, acetic, citric, malic, lactic, fumaric, benzoic, glycolic, gluconic, succinic, p-toluenesulphonic and arylsulphonic acids, for example. Examples of pharmaceutically acceptable base addition salts for use in the present invention include those derived from non-toxic metals such as sodium or potassium, ammonium salts and organoamino salts such as triethylamine salts. Numerous appropriate such salts will be known to those of ordinary skill.

The physician or other health care profesional can select the appropriate dose and treatment regimen based on the subject's weight, age, and physical condition. Dosages will generally be selected to maintain a serum level of compounds of the invention between about 0.01 μg/cc and about 1000 μg/cc, preferably between about 0.1 μg/cc and about 100 μg/cc. For parenteral administration, an alternative measure of preferred amount is from about 0.001 mg/kg to about 10 mg/kg (alternatively, from about 0.01 mg/kg to about 10 mg/kg), more preferably from about 0.01 mg/kg to about 1 mg/kg (from about 0.1 mg/kg to about 1 mg/kg), will be administered. For oral administrations, an alternative measure of preferred administration amount is from about 0.001 mg/kg to about 10 mg/kg (from about 0.1 mg/kg to about 10 mg/kg), more preferably from about 0.01 mg/kg to about 1 mg/kg (from about 0.1 mg/kg to about 1 mg/kg). For administrations in suppository form, an alternative measure of preferred administration amount is from about 0.1 mg/kg to about 10 mg/kg, more preferably from about 0.1 mg/kg to about 1 mg/kg.

For use in assaying for activity in inhibiting glycine transport, eukaryokic cells, preferably QT-6 cells derived from quail fibroblasts, have been transfected to express one of the three known variants of human GlyT-1, namely GlyT-1a, GlyT-1b or GlyT-1c, or human GlyT-2. The sequences of these GlyT-1 transporters are described in Kim et al., *Molec. Pharm.* 45: 608-617, 1994, excepting that the sequence encoding the extreme N-terminal of GlyT-1a was merely inferred from the corresponding rat-derived

sequence. This N-terminal protein-encoding sequence has now been confirmed to correspond to that inferred by Kim et al. The sequence of the human GlyT-2 is described by Albert et al., U.S. Application No. 08/700,013, filed August 20, 1996, which is incorporated herein by reference in its entirety. Suitable expression vectors include pRc/CMV (Invitrogen), Zap Express Vector (Stratagene Cloning Systems, LaJolla, CA; hereinafter "Stratagene"), pBk/CMV or pBk-RSV vectors (Stratagene), Bluescript II SK +/- Phagemid Vectors (Stratagene), LacSwitch (Stratagene), pMAM and pMAM neo (Clontech), among others. A suitable expression vector is capable of fostering expression of the included GlyT DNA in a suitable host cell, preferably a non-mammalian host cell, which can be eukaryotic, fungal, or prokaryotic. Such preferred host cells include amphibian, avian, fungal, insect, and reptilian cells.

As discussed above, the compounds of the invention have a number of pharmacological actions. The relative effectiveness of the compounds can be assessed in a number of ways, including the following:

- **comparing the activity mediated through GlyT-1 and GlyT-2 transporters.** This testing identifies compounds (a) that are more active against GlyT-1 transporters and thus more useful in treating or preventing schizophrenia, increasing cognition and enhancing memory or (b) that are more active against GlyT-2 transporters and thus more useful in treating or preventing epilepsy, pain, spasticity or myospasm.
- **testing for NMDA receptor binding.** This test establishes whether there is sufficient binding at this site, whether antagonist or agonist activity, to warrant further examination of the pharmacological effect of such binding.
- **testing the activity of the compounds in enhancing or diminishing calcium fluxes in primary neuronal tissue culture.** A test compound that increases calcium flux either (a) has little or no antagonist activity at the NMDA receptor and should not affect the potentiation of glycine activity through GlyT-1 transporter inhibition or (b), if marked increases are observed over GlyT-1 inhibitors used for comparison and that have little direct interaction with NMDA receptors, then the compound is a receptor agonist. In either of the above-described cases, the test confirms activity in treating or preventing schizophrenia, increasing cognition, or enhancing memory. In contrast, a test compound that decreases calcium flux has a net effect wherein receptor antagonist activity predominates over any activity the compound has in increasing glycine activity through inhibiting glycine transport. In this case, the test confirms activity in limiting or preventing the cell damage and cell death arising

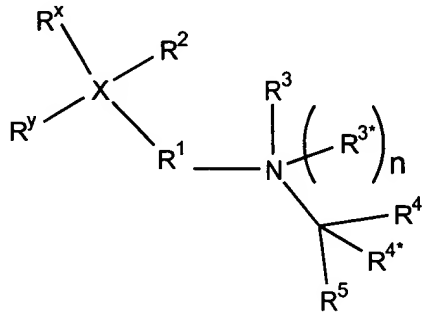
after stroke or other ischemia-inducing conditions, or in limiting or preventing the cell damage associated with neurodegenerative diseases.

All animal methods of treatment or prevention described herein are preferably applied to mammals, most preferably humans.

The following examples further illustrate the present invention, but of course, should not be construed as in any way limiting its scope.

ABSTRACT

The invention provides a pharmaceutical for treatment of neurological and neuropsychiatric disorders comprising a compound of the formula:



or a pharmaceutically acceptable salt thereof.